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ABSTRACT

This review of the developmental readiness of normal, full-term infants to progress from exclusive breastfeeding to the introduction of complementary foods is the result of the international debate regarding the best age to introduce complementary foods into the diet of the breastfed human infant. After a list of definitions, four papers focus on: "Immune System Development in Relation to the Duration of Exclusive Breastfeeding" (Armond S. Goldman); "Gastrointestinal Development in Relation to the Duration of Exclusive Breastfeeding" (W. Allan Walker); "Infant Oral Motor Development in Relation to the Duration of Exclusive Breastfeeding" (Audrey J. Naylor, Sarah Danner, and Sandra Lang); and "Maternal Reproductive and Lactational Physiology in Relation to the Duration of Exclusive Breastfeeding" (Alan S. McNeilly). (SM)

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April 2001

Audrey J. Naylor, MD, DrPH, Editor
Ardythe L. Morrow, PhD, Co-Editor

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Introduction and Background

This review of the developmental readiness of normal full term infants to progress from exclusive breastfeeding to the introduction of complementary foods has been undertaken as a result of the international debate regarding the best age to introduce complementary (semi-solid and solid) foods into the diet of the breastfed human infant. Since 1979 the World Health Organization has recommended that normal full term infants should be exclusively breastfed for ***"four to six months"*** Over the two decades since this recommendation was established further evidence regarding the benefits of breastmilk and breastfeeding has accumulated. In addition, there have been increasing reports suggesting an association between discontinuing exclusive breastfeeding prior to six months of age and an increase in infant morbidity and mortality. Throughout the world many professionals as well as a number of governments have concluded that there is sufficient evidence to recommend continuing exclusive breastfeeding for ***"about six months"*** Even within WHO, UNICEF and other international agencies, some documents continue to recommend exclusive breastfeeding for "four to six months" while others now use "about six months." There is an urgent need to review this matter and determine whether or not there is sufficient scientific evidence to change the global recommendation. WHO responded to this need and arranged for a review of the recent studies that relate duration of exclusive breastfeeding ("four to six months versus six months") to infant morbidity and mortality as well as growth and maternal health.

Another relevant aspect of this global concern needing further attention relates to the infant's internal biologic processes that are proceeding along largely genetically predetermined developmental pathways. These begin at the moment of conception and continue throughout life. A number of these developmental processes are important to infant feeding. The human neonate is delivered from a protected intrauterine environment–sterile, warm, and protective–following nine months of development during which the nutritional, immunologic and endocrine needs were provided for by maternal systems. The newly born infant can no longer obtain fluids, nutrients, and immune protection through the umbilical cord. The ambient temperature is no longer held at maternal body temperature and the environment is no longer sterile. Though this transition is filled with life threatening hazards, there are many biologically active protective systems in place to increase the likelihood of infant survival, some within the infant and some provided by the mother. Obvious and increasingly well understood is the ability of the normal mother-infant dyad to continue the flow of nutrients, fluids, immune substances and other biologically essential and active substances through frequent breastfeeding beginning very shortly after birth. This mother-baby interdependency works remarkably well for a number of months while the infant proceeds with its internally driven biological processes of growth and development. While some of these processes are very visible (physical growth, neuromotor development) others of equal importance are progressing without clear signs. Renal, hepatic, neurologic systems are gradually maturing. The infants own gastrointestinal tract and immune system are becoming more prepared to become independent of maternal resources. Oral motor abilities are also steadily progressing in preparation for the time when breastmilk alone will no longer be able to fulfill all infant nutritional and fluid needs. New oral motor functions will be called into action to assure successful continuation of the intake of foods and fluids.

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Specific Purpose of these Reviews

It is with such biologically driven infant developmental processes in mind that the current reviews have been undertaken. The rationale for these reviews is that each process undergoing development during the first year of a human infant's life will reach a stage where the infant is biologically and developmentally most ready for the introduction of foods other than breastmilk. In addition it seems reasonable that the age of this readiness for both diet and behavioral changes is similar for each of the developmental processes. In other words, it is likely that there is a convergence of the developmental maturation of these processes such that all systems are "ready" at the same time.

The reviews do not focus on health outcomes associated with discontinuing exclusive breastfeeding at a particular age but rather on the biologic/developmental ***readiness*** for this complex experience. Four processes or functions were selected for inclusion: gastrointestinal, immunologic, oral motor and the maternal reproductive processes that relate to the continuation of lactation and the provision of breastmilk.

Process Utilized for these Reviews

Contributors invited to participate as reviewers and authors are well-known experts in their particular area of expertise. After individual papers were drafted, each reviewer had an opportunity to read all papers. A meeting (via teleconference) was then arranged to discuss the findings and consider the following:

- Do the reviews provide evidence regarding the age at which the normal full term infant is developmentally ready to discontinue exclusive breastfeeding and begin receiving complementary foods?
- Is there evidence of the convergence of the age of readiness of the several developmental processes?

To allow readers to draw their own conclusions concerning these questions, each of the four reviews that follow is presented as an independent contribution. The reader may turn to the summary and conclusion section, pages 35-36, for the results of the teleconference.

Definitions

Certain terms used throughout this review are defined here to ensure clarity for the reader:

- Exclusive breastfeeding is the provision of breastmilk only, with no other liquids or foods given.
- Full breastfeeding is defined as the provision of breastmilk, with only water, tea or juice given in addition to breastmilk.
- Complementary feeding is defined as giving solid or semi-solid foods in addition to breastmilk.

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Immune System Development in Relation to the Duration of Exclusive Breastfeeding

Armond S. Goldman, MD

Introduction

The optimal length of exclusive breastfeeding by full-term infants has been estimated from clinical outcomes such as growth, development, and susceptibility to infectious diseases. Indeed, there is evidence from epidemiological investigation that exclusive breastfeeding for about 6 months affords greater health benefits than exclusive breastfeeding for a shorter duration. However, few investigations have been designed to ascertain the optimal duration of exclusive breastfeeding, whether from an epidemiologic or basic science perspective.

One approach to the question would be to ascertain when the human immune system becomes fully mature. To explore that approach, three interrelated questions were posed in this review, as follows.

1. When does the immune system of a well, term infant no longer require the effects of exclusive breastfeeding for its complete development?
2. Are there upper and lower limits of the age of immunological readiness that are dependent or independent of breastfeeding?
3. Does the age of readiness of the immune system converge with the age of readiness of other major organ-systems such as the gastrointestinal tract?

To examine these questions, it is helpful to first consider the organization and complexities of host defenses, general concepts of developmental immunology, the known developmental delays in the immune system, and the agents in human milk that seem to compensate for those developmental delays.

The Immune System

The external environment is first encountered by the skin, the respiratory tract, and the alimentary tract. Each of these vital systems is exposed to environmental pathogens. Innate and specific adaptive defenses have evolved to protect those vital structures as well as systemic sites that may become invaded if first lines of defense at the skin or mucosa fail.

Innate Defenses

Innate defenses are produced in the absence of antigenic exposures, and their protective effects are not necessarily specific just for the encountered foreign agent. These defenses are particularly important during first contact with a microbial pathogen. Innate defenses include structural barriers (skin and its secretions; the epithelium of the gastrointestinal and respiratory tracts), myeloid cells, and soluble agents including gastric HCl, mucin, lactoferrin, and lysozyme in external secretions and complement components in the systemic circulation.

In addition, certain defense agents produced at low levels by unstimulated leukocytes are greatly enhanced in their production once the cells are activated. Some examples include the production of interferons by virus-infected cells, the synthesis of proinflammatory cytokines by monocytes stimulated by bacterial lipopolysaccharides, the generation of toxic oxygen radicals by neutrophils during phagocytosis, and the liberation of active fragments of complement components after activation of the classic or alternative pathways of the complement system.

Specific Adaptive Immunity.

Specific adaptive defense involves protective agents that react specifically with antigens; these protective agents increase after the host is exposed to the antigens. These protective agents are members of a superfamily of protein molecules that are typified by antibodies, which are designated as immunoglobulins (Ig). Other members of the immunoglobulin superfamily include major histocompatibility (MHC) molecules that bind small peptides or antigen fragments that are presented to antigen receptors on T cells in the context of MHC molecules.

Even though specific adaptive immunity and innate immunity are often presented as separate processes, they are closely related in that specific immunity may lead to an augmentation of innate defenses and conversely some types of innate immunity influence the function of cells that produce antigen recognition molecules. The origins, main physical features, and function of antigen recognition molecules are as follows.

B Cells and the Generation of Antibody Diversity.

A repertoire of genes is responsible for the enormous diversity of antibody molecules and hence for their recognition of a wide spectrum of antigenic determinants. There are genes for joining (J), diversity (D), variable (V) and constant (C) regions of immunoglobulin molecules. The complete immunoglobulin gene and antibody diversity are created when one member of each of these categories of genes is selected and spliced together. Complete IgM molecules are produced by B cells found in blood. The resultant IgM antibodies are not glycosylated and therefore not secreted. Instead, they remain on the surface of B cells where they act as antibody receptors for antigens. Antigen binding specificity is found in all antibodies on the surface of each B cell. Further antibody diversity is created by somatic mutations of B cells in germinal centers. B cells that produce higher affinity antibodies are selected for survival.

When surface immunoglobulin molecules on B cells are cross-linked by antigens, the cells proliferate and are transformed into plasma cells that secrete antibodies with the same antigen-binding specificities as the cell surface antibodies. If the host is repeatedly immunized, the class or isotype of the immunoglobulin switches from IgM to IgG, IgA, or IgE depending upon the types of modulating agents that influence the selection of C-region genes of B cells.

Immunoglobulins.

Immunoglobulins are four-chain, globular glycoproteins produced by the B-cell lineage. Immunoglobulin monomers are composed of an identical pair of light (L) chains and an identical pair of heavy (H) chains. Each L and H chain is in turn comprised of C and V regions. V region

domains bind antigenic determinants, whereas C region domains are responsible for other properties of each chain.

There are five classes, or isotypes, of immunoglobulins. Each of these classes have special biological functions: IgA, IgG, IgM, IgD, and IgE. For example, a type of polymeric IgA called secretory IgA is the predominant immunoglobulin in human milk and other external secretions such as saliva. Secretory IgA is assembled from dimers or trimers of IgA produced by plasma cells at mucosal sites and part of polyimmunoglobulin receptors on the basolateral membranes of epithelial cells. The IgA molecules (usually dimers) complexed with their receptors are transported across the epithelial cells. The intracellular part of original receptor is digested. The rest of the receptor remains complexed with the H chains of IgA. Secretory IgA antibodies are especially directed against microbial antigens encountered at mucosal sites. Furthermore, secretory IgA is adapted to persist and function at mucosal sites because of its innate resistance to intestinal and pancreatic proteolytic enzymes. At mucosal sites, the antibodies neutralize bacterial toxins or interfere with the attachment of bacterial pathogens or their toxins to epithelial cells.

T Cells and Cellular Immunity.

T cell differentiation. Undifferentiated lymphocytes enter the cortex of the thymus where they proliferate and express CD3, TcR, CD4, and CD8 transmembrane molecules. Most of them die in the thymus, while a smaller number lose either CD8 or CD4. $CD4^-CD8^+$ cells or $CD4^+$ $CD8^-$ cells are selected respectively by an interaction with thymic stromal MHC class I (with $CD4^-$ $CD8^+$ cells) or class II molecules (with $CD4^+CD8^-$ cells) to leave the thymus and enter the systemic circulation.

TcR Structure. The TcR structure is similar to an immunoglobulin, but the structure is limited to two different peptide chains. In the vast majority of TcR, there is one α-chain and one β-chain. Each chain also has a V and a C region. The antigen-binding diversity of TcRs is created by a mechanism that is similar to that found in B cells. Consequently, TcRs as well as antibodies have an enormous antigen-binding repertoire, although the TcR repertoire is limited to peptide antigens.

T Cell Populations. Mature T-cells that are $CD4^+$ are helper cells, whereas those that are $CD8^+$ are cytotoxic/suppressor cells. T helper cells are further divided into two subsets according to the cytokines they produce. T helper cells that produce cytokines that lead to cellular immunity by enhancing cytotoxic T-cells and recruiting and activating macrophages are termed Th1 cells. The resultant protection is called cellular immunity. This part of the immune system is particularly important in protection against intracellular infecting agents such as viruses, mycobacteria, and fungi. Those that produce cytokines that enhance antibody formation by the B-cell lineage are termed Th2 cells. Th1 cytokines include IL-1 and interferon-γ, whereas Th2 cytokines include IL-4, IL-6, and IL-10.

Mature T-cells are long-lived and recirculate in the blood, lymphatics, and peripheral lymphoid organs including lymph nodes, spleen, and mucosal sites. Resting T-cells produce only low levels of cytokines, but after they are engaged by antigen producing/presenting cells and stimulated by

certain cytokines, they become activated and produce cytokines that orchestrate many aspects of the immune system.

General Concepts of Developmental Immunology

There are five general concepts of developmental immunology that are useful in considering the questions posed in this review. They are as follows:

1. Some developmental delays in the immune system are rectified relatively soon after birth, whereas others develop much more slowly.
2. Regardless of the rate of development, immunological components of human milk often compensate for or directly influence the rate of development of those parts of the immune system. The development of the immune system therefore cannot be understood unless it is considered in the context of breastfeeding.
3. Certain immunological components of human milk may set in motion a train of developmental events that persist long after breastfeeding ceases. Because the proximity of cause and effect relation is missing, this may lead to uncertainty regarding the optimal duration of exclusive breastfeeding.
4. Even if the development of parts of the immune system are complete, the infant may nevertheless benefit from immunological components in human milk. Secretory IgA antibodies in human milk are such an example. In that case the mother develops specific secretory antibodies in her milk that are directed against the microbial pathogens found in her gastrointestinal and respiratory tracts. These maternally generated specificities augment the child's defenses since those same antigen-binding specificities at the mucosal sites of the infant may not appear in time to ward off an infection. This immunological head start from the mother may therefore be highly advantageous.
5. It is likely that the central question, "When does the immune system of the well term infant no longer require the effects of exclusive breastfeeding for its complete development?," will also have to be considered in respect to the external environment of the infant. The reason is that some environmental agents also affect the rate of immunological development. For example, the production of memory T cells depends upon antigen stimulation as well as certain immunostimulatory cytokines that are released as infecting agents interact with the immune system. It also should be recognized that the environmental load of microbial pathogens may exceed the capacity of the infant's mucosal immune system, whereas the combined protection afforded by the infant's immune responses and the immune factors provided by human milk may suffice.

Developmental Delays in the Human Immune System

The development of the immune system during intrauterine and postnatal life is complex and tightly controlled. In addition and germane to the questions raised in this review, the development of many parts of the immune system is delayed and those delays appear to be compensated for or modulated by maternal factors transmitted via the placenta or the mammary gland. Developmental delays at birth include immunoglobulin isotype switching, the production of IgG antibodies to polysaccharide (T-independent) antigens, the elaboration of lysozyme by epithelial cells, generation of memory T-cells, generation of certain complement components

(C3, C4, C8, and C9), the production of PAF-acetylhydrolase, and synthesis of many cytokines including IL-1, IL-3, IL-6, IL-8, IL-10, TNF-α, interferon-γ, interferon-β, G-CSF, GM-CSF, and M-CSF. In addition, there are developmental delays in certain neutrophil functions and deployment in response to bacterial infections, in the ability of blood monocytes or aveolar macrophages to produce cytokines that aid in the stimulation of T cells, and the capacity of primitive human haemopoietic cells to respond to Flt-3 ligand, Steel factor and IL-3. Moreover, there is considerable variation in the rate of development of different agents. For instance, IgG antibodies to thymic-dependent antigens begin to be produced shortly after birth whereas IgG antibodies to thymic-independent antigens are not made until two years of age.

One word of caution should also be included concerning the interpretation of some of the studies of developmental delays in the immune system. Although decreases in functions may be found in newborn cells, the decrease may be incident to the soluble agents in the plasma that inhibit those functions. For example, the synthesis of interferon alpha by umbilical cord blood monocytes is inhibited by increased cortisol levels in those specimens.

Agents in Human Milk That Compensate for Those Developmental Delays

A host of investigations performed over the past 40 years indicate that the protection afforded by breastfeeding is mainly due to defense agents in human milk, many of which are developmentally delayed in the infant. Other agents in human milk do not directly compensate for developmental delays in the production of those same agents, but nevertheless protect the recipient. For example some enhance functions that are poorly expressed in the recipient, change the physiological state of the intestines from one adapted to intrauterine life to one suited to extrauterine life, or prevent inflammation in the recipient's gastrointestinal tract.

Antiinflammatory, and immunomodulating agents that are adapted to mucosal sites, are often multifunctional, and are not well represented in other milks used in human infant feeding. The antimicrobial factors include secretory IgA, and lactoferrin. The defense system in human milk is comprised of antimicrobial, lysozyme, mucin, glycoconjugates, oligosaccharides, and antiviral lipids generated by partial digestion of milk fat. The antiinflammatory agents involve some of the antimicrobial factors, enzymes that degrade inflammatory mediators, cellular protective agents, epithelial growth factors, and antioxidants. The immunomodulators include nucleotides, cytokines, and antiidiotypic antibodies.

In addition to the soluble and compartmentalized immune agents, human milk, particularly early in lactation, contains many leukocytes (~1-3 x 10^6/mL). About 80% of those cells are neutrophils, 15% are macrophages, and 5-10% are lymphocytes. The vast majority of the lymphocytes are T cells. Furthermore, virtually all leukocytes in human milk are activated. In that respect, the neutrophils and macrophages have an increased expression of CD11b/CD18 and a decreased expression of L-selectin, the macrophages are more motile than blood monocytes, and the T cells display the memory phenotype, CD45RO, and other phenotypic markers of activation. The fate of these cells in the recipient is uncertain, but there is evidence from experimental animal models that milk T cells enter tissues of the neonatal animal. Furthermore, some observations suggest that cellular immunity to tuberculosis or to schistosomal antigens may be transferred to the infant by breastfeeding. Thus, it is possible that some of these maternal cells function in the recipient infant to compensate for certain developmental delays in the T cell system.

Although the agents in human milk that cause immunomodulation *in vivo* are not known, immunomodulatory effects of breastfeeding have been demonstrated. For example in a recent study, 14 days after the live MMR vaccination, only breastfed children had increased production of interferon-gamma and increased percentages of $CD56^+$ and $CD8^+$ T cells. These findings are consistent with a Th1 type response by breastfed children, not evident in formula-fed children.

Are Experimental Animal Models Helpful?

Can we extrapolate from experimental animal models to the human species and thus find answers to the questions posed in this review? Curiously enough, the dearth of information found in the research literature regarding the development of the human immune system also pertains to many other mammalian species. In most species comparatively little is known about the changes in the daily production of many immune factors by the mammary gland as lactation proceeds. Furthermore there are too many differences between non-human mammals and humans except for our most closely related evolutionary relatives, *Pan troglodytes* and *Pan paniscus* (chimpanzees), to apply information from other mammalian species to humans.

The Rates of Development of the Immune System in Exclusively Breastfed Infants

There is very little information in the published scientific literature that tracks the development of immune components of the immune system. Usually the status of newborn infants is compared to much older children or adults and not to older infants or toddlers. Furthermore, no longitudinal investigations have been published. Moreover, the effect of exclusive, partial or no breastfeeding has been difficult to discern from the reports in the literature. In most of the publications the type of infant feeding is not stipulated. In others, the completeness or duration of breastfeeding is not defined.

Although the duration of certain developmental delays is known, it is unclear when optimal levels for other agents are reached. In particular, little is known concerning the developmental patterns of the production of cytokines by not only cells of the hemopoietic lineage such as T cells, B cells, NK cells, monocytes, macrophages, and dendritic cells, but also epithelial cells that line the gastrointestinal and respiratory tracts.

The problem is further compounded by two other large gaps in our knowledge. In most reports concerning the longitudinal patterns of postnatal development of the immune system, the effects of the type of infant nutrition, breastfeeding or non-breastfeeding, are unknown. Furthermore, there is little information concerning the longitudinal patterns of production of many immune factors other than major antimicrobial ones in the human mammary gland. Thus, the relationships between the rates of development of components of the immune system and the capacity of the mammary gland to produce agents that compensate for or influence the developmental delays in the immune system, are not precisely established.

Conclusions and Future Research

At the present time, there is little if any information that provides answers to the questions raised in this review. The subset of issues that should be addressed is as follows.

1. Although a great deal is known, the complete extent of, and controls over, the immune system are yet to be defined.
2. The ontogeny of most of the components of the human immune system has not been investigated.
3. The patterns of developmental delays in the immune system vary according to the component, but the extent of the variability is unknown.
4. The time for the optimal development of each immune factor that is developmentally delayed has not been determined.
5. It is uncertain whether a developmental delay in one factor influences the development of others in the immune system.
6. Certain immunological components of human milk may set in motion a train of developmental events that persist long after breastfeeding ceases. This may cause some uncertainty regarding the optimal duration of exclusive breastfeeding.
7. Even if the development of parts of the immune system are complete, the infant may nevertheless benefit from immunological components in human milk. Therefore, clinical outcome studies would be required to determine the optimal duration of exclusive (or partial) breastfeeding.
8. Environmental agents may also affect the rate of immunological development. Thus the studies would also have to control for those confounding variables.
9. Moreover, the nutritional state of the child (poverty or excess) may be inappropriate for the post-breastfeeding development of the immune system.

It is evident that these types of investigations, though of interest, will be impractical to conduct because of their complexities and expense and ethical issues that preclude invasive procedures in infants and children who are or are not breastfeeding. A compromise would be to investigate a few components of the immune system that are developmentally delayed and that are well represented in human milk. Those investigations would require a great deal of planning and human, laboratory and fiscal resources and they would not definitely answer the question. They would, however, be a logical start.

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Gastrointestinal Development in Relation to the Duration of Exclusive Breastfeeding

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Introduction

This manuscript reviews the development of digestive, absorptive, and protective functions of the human gastrointestinal tract during the first six months of life. Development will initially be considered during intrauterine existence and then during the postpartum period. Emphasis will be placed on those gut functions that remain immature after birth. Evidence will be considered that supports the role of breastfeeding and other extra-uterine, environmental factors that influence the maturation of gut functions. The review will underscore the possible consequences of persistent immaturities of gut function with regard to infant health and susceptibility to disease. Finally, the potential importance of exclusive breastfeeding for the first six months of life will be considered with regard to providing passive factors that may facilitate the efficient function of the immature gut, as well as bioactive factors (hormones, growth factors, cytokines, etc.) that may accelerate the development of the infant's own gut function.

Intrauterine Development

Development of morphologic function of the human gastrointestinal tract progresses rapidly during the first trimester. By eleven weeks postpartum, the multi-layered endothelium has matured into a single layer of polarized enterocytes, and developmental modifications have begun to increase the surface area of the small intestine. During the second trimester, epithelial cells differentiate into specific cell lineages. By the beginning of the third trimester, morphologic development of the gut is virtually complete. Thus, the newborn full-term infant at birth appears to have a fully anatomically developed gastrointestinal tract. Functional development of the human gut however, progresses at a different pace in utero. Intra-luminal digestive enzymes develop slowly; the capacity to digest proteins, lipids, and complex carbohydrates is incomplete at birth and remains so for much of the first year of life. Microvillus enzymes for end stages of digestive function, e.g., sucrase-isomaltase, lactase, and trehalase, slowly develop during the second and third trimester. Because of a paucity of human tissues for study during the third trimester, the development of mucosal nutrient carriers for amino acids, fatty acids, and monosaccharides are not completely understood, however, it is postulated that by birth the small intestine has about 75% of its fully developed capacity to transport these nutrients across the microvillus surface.

In order for "succus entericus" to be digested and absorbed, it must be mixed with intestinal secretions and moved sequentially along the small and large intestine for maximal absorption before final elimination by defecation. This process requires a coordinated peristaltic movement, i.e., rhythmic contractions of smooth muscle in a cephalad to caudal direction. In general, the enteric nervous system and intestinal smooth muscle are developed in utero and are functional at term. However, the subtle activity of sphincter and peristaltic contractions is not completely

developed at birth because of the delayed appearance of neurotransmitter receptors and other mediated trophic factors released by proteins, lipids and carbohydrates in the enteric contents.

Another important capacity of gut function is the host defense system that protects the enormous epithelial surface area against the uptake of pathologic microorganisms and foreign antigens. At full-term, the gut epithelium and lymphoid compartments are almost completely developed, including the lymphoid aggregates in Peyer's patches and the microfold cells (M-cells) overlying these patches to sample luminal antigens, T cells and microphage in the lamina propria and intra-epithelial lymphocytes between enterocytes. However, for an appropriate efferent response of these mucosal immune components, the gut must leave the sterile intrauterine environment and enter the extra-uterine environment containing microorganisms and foreign antigens. In the maturation of mucosal immunity the crucial first step is initial bacterial colonization. The nature of this colonization is an important determinant of the infant's ability to prevent inappropriate immune responses to stimulation, e.g., inflammatory and allergic reactions.

Extra-Uterine Development

At birth, the newborn enters the extra-uterine environment where the gastrointestinal tract must function independently from the maternal capacity to provide nutrient and immune protection in utero. As previously stated, at term, the human newborn's gastrointestinal tract is anatomically mature and has the capacity to assume most of the digestive, absorptive, and protective functions. However, several subtle immaturities of these functions require the ongoing dependence on maternal help via the ingestion of colostrum and then mature breast milk, because luminal enzymes provided by release of pancreatic secretions is not yet coordinated. The digestion of proteins, lipids and complex carbohydrates is immature. Efficient breakdown of lipids to fatty acids for absorption is impaired by a decreased lipase activity. In like manner, the breakdown of protein to amino acids and the breakdown of complex carbohydrates to monosaccharides are altered by low levels of proteases and amylase, respectively. Although some suggest that the mucosal surface active transport of fatty acids, amino acids and monosaccharides are sufficiently developed to provide adequate transport across the gut and into the newborn circulation, the process has not been studied in detail. In addition, other luminal mucosal immaturities may affect efficient utilization of enteric nutrients, including the uptake of iron (Fe^{++}) and zinc (Zn^{++}). At birth the capacity of the newborn to produce acid for secretion into the stomach is hampered by an immature receptor response to enteric hormones such as pentagastrin. This immaturity, along with the lack of coordinated peristalsis in the small intestine, allows for excessive colonization of the small intestine with ingested bacteria. Increased levels of bacteria in the small intestine can cause a diversion of nutrients to bacteria and thereby provide less for digestion and absorption across the infant's intestine. Furthermore, breakdown products of bacterial metabolism include production of short chain fatty acids such as butyrate which can have serious effects on mucosal inflammatory responses. Other dysmotilities in newborn gut function can hamper efficient digestion and absorption. For example, all newborns have a physiologic regurgitation of ingested food because of the immaturity of the lower esophageal sphincter, due to a poor response to hormonal stimulation. In addition, the newborn infant's stomach does not release its content via the pyloric sphincter in a coordinated fashion. This combination of immature motility responses can lead to regurgitation, inefficient small intestinal digestion and absorption, and aspiration pneumonitis.

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Intestinal defenses, particularly the mucosal immune system, are, for the most part, intact and capable of response to luminal stimuli at birth. However several aspects of the mucosal immune response remain immature, making the infant susceptible to specific gastrointestinal and systemic diseases. In order for the newborn's mucosal immune system to function properly, it must have the appropriate environmental luminal stimuli. This means that the newborn gut must establish via initial colonization a stable intestinal flora which is the primary stimulus for an efficient immune response. The nature of colonizing bacteria can determine whether the gut immune system results in bacterial infection and inflammation or an intact mucosal defense which prevent these disease processes. At birth, the capacity of plasma cells in the lamina propria to release polymeric IgA (pIgA), the principal protective immunoglobulin in secretions, in response to luminal stimuli is immature; it takes several months to a year for protective levels of pIgA to appear in intestinal secretions. In essence, the newborn infant is pIgA deficient and therefore susceptible to the same diseases as genetically pIgA deficient individuals, e.g., intestinal infections and systemic allergy.

In addition, the intrauterine environment favors a T helper cell response in newborns that is Th2 predominant. Th2 helper cells produce a cytokine response (IL4, IL5, etc.) that favors humoral immunity and antibody responses, including IgE. While this imbalance in Th subclasses may favor the protection from rejection of the fetus in utero, it creates problems in the extra-uterine environment. In the absence of a balance in the Th responses between Th1, Th2, and Th3, cells can, in allergy-prone infants, lead to atopic food allergy. A proper balance in Th subclasses is achieved by appropriate colonization of the infant's gut, as found to occur with exclusive breastfeeding. In addition, the immature intestinal epithelium allows the absorption of intact proteins and peptides that can contribute to inappropriate systemic immunologic responses, further contributing to the development of intestinal food allergy in young infants.

As part of the fetal/newborn immune response both in utero and in the extra-uterine environment, the immature gut reacts to luminal stimuli by over-responding with sustained inflammation. This increased propensity to inflammation may be an important defense for the premature neonate and infant against adverse effects of microbial penetration, but it also has its drawbacks. For example, the immature inflammatory response to microbial stimuli is considered an important risk factor to the development of necrotizing enterocolitis in the premature infant and specific infectious gastroenteritis in the older infant.

An important component of the neonatal mucosal response is systemic non-responsiveness to the ingestion of foreign antigens such as cow's milk protein. This response is termed oral tolerance. The young infant lacks the capacity to produce oral tolerance. If this immaturity exists beyond the newborn period, infants can develop diseases such as allergy and autoimmunity. Oral tolerance is not completely understood at present but is hypothesized to be due to the development of appropriate antigen presentation by antigen presenting cells to T helper cells in such a way that cytokines can down regulate systemic humoral and cellular responsiveness to that antigen. Maturation of the infant's gut to develop oral tolerance requires an appropriate bacterial colonization and a balance of T helper cells (Th1 vs. Th2 vs. Th3). A failure to provide proper extra-uterine luminal environmental stimuli may delay maturation of the infant's intestinal defenses and could predispose the infant to age-related diseases in infancy and later childhood.

Role of Human Milk in Gut Function

Since the development of gastrointestinal digestive, absorptive, and protective function with the birth of the full-term infant is almost complete, obvious reasons to promote exclusive breastfeeding for the first six months of life are not apparent. That is, infants not breast-fed or partially breast-fed for that period do not necessarily develop life-threatening diseases nor do they become obviously severely malnourished. However, as we understand the subtle immaturities in the human infant's gut function after birth and the factors in human milk that facilitate gut function and stimulate a rapid development of mature infantile gut function, a strong argument for exclusive breastfeeding can be made.

As stated previously, the ingestion of mother's colostrum and mature milk can be considered an extended maternal influence over the infant into the extra-uterine environment. We know from several reviews that the composition of maternal milk differs from mothers delivering prematurely, in colostrum, and in mature milk. For example, the composition of colostrums and mature milk from mothers delivering prematurely favors factors more appropriate for the premature and newborn infant, e.g., higher concentrations of pIgA, cytokines and growth factors. In addition, there is evidence that human milk ingestion passively and actively facilitates appropriate function of the infant's gastrointestinal tract.

Intraluminal digestion of lipids, protein, and complexe carbohydrates is incomplete at birth and during infancy. Human milk contains enzymes, such a lipase, that facilitates efficient digestion of these foods. In addition, the lipid, protein, and carbohydrate composition of human milk is appropriate for the combined digestive capacity of human milk itself in the infant's luminal enzymes, thereby more effectively dealing with immature luminal digestion. The surface of the small intestine epithelium and its transporters of end stage digestive products, e.g., fatty acids, amino acids and monosaccharides, appears to be appropriate for neonatal absorption of nutrients. However, efficient transport of trace metals essential to normal metabolic function of the newborn may be incomplete. There is evidence to suggest that human milk contains soluble transporters for iron (Fe^{--}) and zinc (Zn^{--}) that can more efficiently facilitate the absorption of these ions, which milk may account for the normal levels of these trace elements in the circulation of breast-fed infants, even though human milk itself contains low levels of these trace metals.

Although not completely studied, there is evidence that breast-fed infants appear to have a more coordinated motility of their gastrointestinal tract and less difficulty with esophageal regurgitation, gastric emptying, or elimination of waste. The basis for this observation is at this point speculative but may be explained by the composition of human milk nutrients, e.g., non-digestible oligosaccharides whose breakdown products can stimulate gut motility.

In this review, a strong emphasis has been placed on the initial colonization of the gut as an important environmental, luminal factor to the appropriate development of mucosal defenses, particularly mucosal immune responsiveness. Human milk ingestion facilitates the colonization of the gut with bacterial flora that activate the mucosal immune response to luminal antigens. The presence of "bifidous factor" and non-digestible oligosaccharides in human milk facilitates a bacterial flora rich in lactobacilli and bifido bacteria organisms. These factors facilitate the production of lactic acid which results in an acid milieu in the gut (pH=5) favoring the

proliferation of lactobacilli. Non-digestible human milk oligosaccharides are metabolized by small intestinal bacteria to produce short-chain fatty acids which maintain this same milieu. Oligosaccharides also can inhibit the attachment of pathogens to glyconjugates on the intestinal surface as a first step in invasion. These human milk factors are currently under investigation as "prebiotics," i.e., nutrients that facilitate the production of "good bacteria" or probiotics. By facilitating the growth of health-promoting intestinal bacteria, the gut also develops a balance between T helper cells. A clinical study in Finland has shown the beneficial effect of lactobacilli given to infants with allergic dermatitis to food allergens in reducing IgE mediated response.

As noted above, the immature fetal and newborn gut over-responds to luminal stimuli by an excessive sustained inflammatory response, which can predispose infants to gastrointestinal disease. Human milk contains multiple anti-inflammatory molecules (TGFβ IL-10, PAF acetylhydrolase) that down regulate excessive inflammatory responses in the immature intestine until the infant's own intestinal host defenses develop. The anti-inflammatory protection of the infant's gut may be very important in the prevention of symptomatic infection and inflammatory diseases during infancy. The most obvious example of human milk providing both passive and active protection to the infant's gut involves pIgA. While the full-term infant is relatively pIgA deficient for the first months of life, the pIgA in human milk is directed against the infant's intestinal antigens. Colostrum contains high concentrations of pIgA which decrease in mature milk. Human milk also contains growth factors and cytokines that facilitate the maturation of IgA-producing plasma cells in the infant lamina propria.

Furthermore, several studies have suggested that specific nutrients abundant in human milk may be effective as protective nutrients important in the maturation of the infant's intestinal defenses. For example, human milk contains large quantities of nucleotides. Under conditions of stress, e.g., entering the extra-uterine environment, exogenous nucleotides may become conditionally essential nutrients. Exogenous nucleotides may facilitate enterocyte proliferation and differentiation, enhancing mucosal and systemic immune and cellular responsiveness. Omega-3 fatty acids exist in human milk and may exert anti-inflammatory effects with a decreased production of prostaglandins and inflammatory cytokines by their incorporation into the cellular lipid membrane of lymphocytes and enterocytes. Lactoferrin in human milk has antibacterial effects (competing for iron with luminal bacteria) and anti-inflammatory effects directly interfering with the transcription of TNFα, mRNA, etc., in the nucleus of enterocytes and lymphocytes. These examples of protective nutrients illustrate the importance of further defining the function of human milk nutrients during the first six months of life.

Summary and Conclusions

In this review of gut development, the maturation of gastrointestinal digestive, absorptive, and protective function has been examined during gestation. In general, the human gut is anatomically and functionally mature at birth in the full-term infant. However, subtle immaturities in luminal digestion, mucosal absorption and protective function exists at birth that may predispose the infant during the first six months of life to age-related gastrointestinal and systemic diseases. Since access to gastrointestinal tissue during the third trimester and during infancy is problematic, a complete understanding of immaturities is lacking. However, it is suggested that exclusive breastfeeding provides both passive and active support of the infant's gut function during the first six months of life as an extra-uterine extension of maternal influence

over the fetus in the intrauterine environment. Several examples are provided of the benefit of human milk ingestion facilitating the immature infant gut function in a more efficient fashion. This review provides objective evidence supporting the recommendation that infants should be exclusively breast-fed up to the sixth month of life.

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Infant Oral Motor Development in Relation to the Duration of Exclusive Breastfeeding

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Introduction

Effective oral motor function is fundamental to a newborn human infant's successful transition from intra to extra-uterine phases of life. The development of this function begins prenatally. By the completion of gestation the fullterm newborn infant is prepared to successfully transfer colostrum and soon thereafter maternal milk with its more "mature" nutritional and immunological profile from its mother's breasts through its oral cavity to the intestinal tract. As the newborn grows older there is a need to progress from the liquid intake of neonates and young infants to the increasingly solid diet of the older infant and young child using hands, spoons or other devices. Throughout the first 12 months after birth oral motor function progressively develops to match other biologically driven developmental processes. The following discussion reviews the current understanding of the development of oral motor function. Of particular interest will be to consider at what postnatal age the normal term infant is developmentally ready to discontinue exclusive breastfeeding and begin the intake of semi solid and solid complementary foods.

Oral Anatomy and Function

Anatomical structures of importance to oral motor function include the oral cavity, the lips, the upper and lower jaw, the tongue, cheeks, the hard and soft palate, the hyoid bone and thyroid cartilage, the epiglottis, the constrictor muscles of the pharynx and more than 40 other muscles as well as six cranial nerves (I, V, VII, IX, X, and XII). These structures participate in a complex process of transporting both food and air through the oral cavity. Sucking, chewing and tongue activity prepare food for swallowing. Within the pharnyx both liquid and solid foods are swallowed and guided into the esophagus while air moves toward the larnyx and trachea. This process requires a sequence of well-coordinated neuromuscular actions. Additionally adjustments are occurring as the infant grows, develops and matures both anatomically and neurologically.

A number of important differences exist between the anatomy of the newborn and that of the older child and adult including:

- the oral cavity and lower jaw (mandible) is smaller than in the older infant and adult
- the lower jaw is slightly retracted
- sucking pads, (fatty tissue deposits within the cheek muscles), contribute to limited space and provide a degree of important stability for early sucking efforts
- oral space restrictions result in the tongue filling the space and in restricting its movement

- airway protection is more anatomically assured due to higher position of the larynx and the close approximation of the epiglottis and soft palate.

Newborn and Young Infant Feeding Reflexes

In addition to the anatomical differences described in the previous section, full term infants begin their extra-uterine life with five important prenatally developed reflexes well in place, including swallowing, sucking, gag, phasic bite and rooting. These reflexes, which fade or disappear altogether during the first year, are the basis for the development of successful lifelong oral motor function. Each will be briefly described.

Swallowing is present in the fetus by the end of the first trimester, considerably earlier than sucking. The fetus is reported to have much experience with this important oral motor function, having swallowed significant amounts of amniotic fluid prior to delivery. While reflexive sucking fades over the first few months after delivery, swallowing, triggered by liquids or solids in the oropharnyx, remains present throughout life.

Sucking becomes evident in the fetus by the middle of the second intrauterine trimester. It can be elicited in the newborn by touching the lips, cheeks, and inside of the mouth including the tongue, gums, hard palate and mucous membranes. When stimulation is initiated by an object in the infant's mouth (e.g., finger, mother's nipple) the infant extends the tongue over the lower gum, raises the lower jaw and initiates the sucking sequence. By about three months sucking becomes decreasingly automatic and more voluntary.

The ***gag reflex*** is present early in the third trimester and is stimulated when the posterior two thirds of the tongue or the pharyngeal wall is touched. The reflex is less intense after about six months of age but does not disappear. The area of stimulation, however, gradually decreases to about a quarter of the posterior tongue.

The ***phasic bite reflex***, also present early in the last trimester, results in the rhythmical opening and closing of the jaw when the gums are stimulated.

Rooting, the last reflex to appear prenatally, is a side-to-side head turning and the wide opening of the mouth. This response occurs when the skin surrounding the mouth is stroked. It assists the infant in locating the breast and nipple and preparing to attach. It is usually most notable when an infant is hungry. In the normal infant this reflex is no longer present after about 3 months of age.

Development of Oral Motor Function

The described anatomical structures and reflexes of the newborn infant contribute to assuring successful initiation of oral feeding essential for neonatal survival. Early studies using cineradiography and more recent (and safer) real-time ultrasound techniques, provide images of the anatomy and reflexive events occurring within the oral cavity of the neonate during the intake and transporting of food and air. These studies demonstrate that normal full term newborn infants apply the dorsum of their tongue to the mother's nipple and surrounding areola. Then, almost simultaneously, an anterior-posterior peristaltic wave-like contraction of the tongue and depression and vertical grooving of the posterior portion of the tongue occur, as well as contraction of the lower jaw (mandible), drawing the nipple and areolar tissue into the mouth to

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the junction between the hard and soft palate. The mandible (and thus the gums) holds the nipple in place and compresses the lactiferous sinuses. This combination of tongue and jaw action expresses milk from the nipple into the mouth. The negative intra-oral pressure and space resulting from the depression and grooving of the posterior tongue and subsequent relaxing of the mandible, causes the milk to move toward the posterior oral cavity and briefly collect in the groove formed near the back of the tongue. The lower jaw then relaxes and lowers. This further increases the negative intra oral pressure. The peristaltic wave of the tongue moves away from the nipple, presses against the soft palate and seals the milk within the oropharnyx and stimulates swallowing. During swallowing the muscles of the palate and oro- and hypo- pharyngeal regions close the nasal cavity. The laryngohyoid complex, arytenoids and backward movement of the epiglottis close the airway. Breathing is briefly interrupted as the milk passes into the upper esophagus stimulating peristaltic contractions and moving the milk into the stomach. Breathing is then resumed and the sequence of suck-swallow-breathe begins again. This suck-swallow-breathe sequence is considered to be well developed by about 37 weeks of gestation and prepares the term infant to begin breastfeeding immediately after birth.

The rapidity of the sequence varies with the intensity of hunger as well as the stage of the particular feed. Early in a breastfeeding episode, sucking is more rapid. As the maternal milk ejection reflex begins to activate and milk flow occurs, sucking slows down. The amount of milk flowing influences the strength and bursts of sucking and pausing.

As the first year of life progresses, the biologically driven oral motor development of the infant assures successful transition from the liquid intake of neonates to the solid foods needed by the older infant, child and adult. The disappearance of rooting and sucking reflexes along with significant changes in anatomy occur in preparation for this transition. Many oral motor specialists consider sucking as the oral stage of swallow and the intake stage of eating liquids and semisolid foods. Two phases of sucking development are evident as the infant progresses, ***suckling*** and ***sucking***. The major distinction between these phases relates to the movement and configuration of the tongue.

During ***suckling*** the tongue musculature moves in a backward-forward peristaltic wave and stripping action which helps to draw out liquid from mother's breast into the infant's mouth. (The cine and ultrasound studies noted previously described suckling.) ***Sucking*** is a more mature behavior and emerges gradually between six and nine months as the anterior tongue motion shifts from the backward - forward movement to an increasingly voluntary and refined up and down motion. A new type of swallow also appears which can be initiated without a preceding suckle to move the tongue in a backward direction.

The change in tongue movement to an up-down motion is accompanied by anatomical alterations leading to an increase in the vertical space in the oral cavity. This increase in space results from growth of the infant's head, increasingly downward movement of the lower jaw, and the absorption of the fat pads of the cheeks. Increase in space also allows for greater lateral tongue movement. As the up-down and lateral movement gradually replace backward-forward tongue action, the deep grooving of the posterior tongue, previously needed to channel a liquid bolus, also diminishes allowing for additional lateral tongue movement. Thus between six and nine months it becomes possible for infants to receive semisolid foods without reflexively pushing these foods out and to effectively collect a bolus of food, move it about in their mouths, and

direct it to the posterior portion of the tongue. There swallowing is triggered and the bolus is then transferred to the esophagus and finally into the stomach.

In addition to the anatomical growth and changes in reflexive responses which contribute to an infant's oral motor ability to successfully transition from liquids to semi-solid and solid foods, there are important changes in proximal (central) musculature resulting in greater strength and stability of trunk, shoulder and neck muscles. These relate to the development of the ability to independently control the head and to sit up. In addition, they contribute to the development of fine motor coordination of more distal muscles including the tongue and lips and their function in bringing in and manipulating more solid food in preparation for swallowing. This development of proximal musculature occurs at or after six months.

Summary and Conclusion

This review of the development of infant oral motor function was undertaken to understand the processes taking place during gestation and over the first six to nine months after birth which assure effective oral intake throughout this phase of life. It was also of interest to determine when the oral motor function of normal human infants was developmentally ready to transition from an entirely liquid intake to the inclusion of semi-solid or solid foods. Four aspects of oral motor development were included in the review:

- A description of oral anatomy and recognized differences between that of the neonate and of older infants, children and adults.
- A description of the oral reflexes of the newborn and young infant and important changes occurring during the first six to nine months which facilitate successful transition from an exclusive liquid oral intake to semi-solid and solid foods.
- A description of the development of oral motor function in terms of the interplay between the biologically driven changes in oral anatomy and neonatal reflexes related to initially transferring liquids from the oral cavity to the esophagus and later to transferring solid food materials.
- A brief commentary regarding the importance of the development of increased strength of proximal musculature (trunk, shoulder and neck) as it relates to head control and coordination of tongue and lip function essential to effectively bring semi-solid and solid foods into the intra-oral cavity, move them about and prepare them for swallowing.

Though formal case control studies concentrating on the longitudinal development of oral motor function are limited, considerable work has been done regarding overall infant neurologic development. These reports combined with extensively reported clinical experience from specialists in infant oral motor development and therapy provide strong indication that under normal circumstances, oral motor function is developmentally ready for the introduction of semi-solid and solid foods and thereby the discontinuation of exclusive breastfeeding between six and nine months of age. While infants can be offered such foods at an earlier age, their oral anatomy, reflexive responses and resulting oral motor function indicate that this is developmentally premature and may increase the risk of aspiration.

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Maternal Reproductive and Lactational Physiology in Relation to the Duration of Exclusive Breastfeeding

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Introduction

The concept that there might be a right time, in terms of the reproductive physiology of either the mother or the baby, for the mother-baby unit to cease exclusive breastfeeding is extremely difficult to determine. Clearly, if the mother decides not to breastfeed at all then the mother totally controls the destiny of the baby. Conception in the absence of contraceptive cover can occur within six weeks postpartum, with an inter-birth interval of less than 12 months. This may have a disastrous effect on the baby depending on family circumstances, with infant morbidity and mortality being directly related to short inter-birth intervals. However, the scope of this paper is the consequence of breastfeeding on fertility and so I will not address the non-breastfeeding situation further. There is no dispute that exclusive breastfeeding can maintain infertility in the mother for prolonged periods. In the absence of natural or artificial contraceptives inter-birth intervals of four years or more have been recorded. While this may be the extreme, it illustrates that the continued suckling of the baby is more than capable of sustaining an effective block to resumption of fertility in the mother. This gives the obvious advantage to the growing infant in that there is no direct competition with another sibling for the attentions of the family in the upbringing of the baby.

On the other hand it is also clear that the biological effect of breastfeeding on suppressing fertility is a very rapidly removed suppressor. Once the reproductive system of the mother has returned to normal, then any abrupt decline in suckling will result in a rapid return of ovulatory cycles and pregnancies may occur without any intervening menstrual period. It would be presumed in this case that it is the biologic will of the mother to replace any infant no longer capable of suckling–through for example major illness or death–with a new sibling, and so passing on her/their genes.

If this is the case then it is the baby who is controlling when fertility resumes in the mother, and the mothers reproductive system is being controlled entirely by the suckling of the baby. The point at which the suckling stimulus declines to a level at which fertility returns in the mother is quite variable amongst women. It is clear now from the major studies on the use of lactational amenorrhea method (LAM) that exclusive breastfeeding prevents almost all pregnancies for at least six months, and is certainly very effective up to nine months. Of course the decision as to when suckling patterns change to such an extent that the suckling stimulus declines below the level capable of suppressing fertility is not directly controlled by the infant.

It appears from limited studies that the amount or strength of suckling undertaken by the baby relates to several factors which may or may not be correlated:

- the ease of milk let-down

- the amount of milk available
- the amount of nutrition other than breast milk that the baby receives, although this obviously is not an issue when there is exclusive breastfeeding.

It is perhaps time to review the mechanisms whereby sucking does switch off or modulate the reproductive axis in women since there may be better clues as to whether there really is a right reproductive time for full breastfeeding to no longer be required.

The Endocrinology of the Normal Menstrual Cycle

The normal menstrual cycle is controlled by GnRH (Gonadotropin Releasing Hormone), the hypothalamic hormone that controls the production of the pituitary gonadotrophins, Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH). GnRH is released as pulses approximately every hour, except at mid cycle where release is continuous to facilitate the preovulatory LH surge. FSH stimulates ovarian follicle growth while LH stimulates steroid production by the follicle, and subsequently by the corpus luteum formed from the follicle after ovulation. Ovulation of the preovulatory follicle is induced by a massive release of LH from the pituitary, the preovulatory LH surge, triggered in turn by a sustained large release of GnRH from the hypothalamus induced by the rising levels of estradiol secreted by the dominant preovulatory follicle. Before the preovulatory LH surge, estradiol, secreted by the follicle, is generated by a continuous release of LH pulses released at approximately hourly intervals. Blockade of this pulsatile secretion is known to stop ovarian steroid production and cause infertility. Furthermore, the release of FSH is regulated by the negative feedback effects of estradiol and inhibin secreted by the developing and dominant follicles, which leads to a suppression of FSH secretion. Thus in the normal cycle, FSH secretion is suppressed during the luteal phase of the cycle due to the steroid and inhibin feedback from the corpus luteum of the cycle. Around menses, when the corpus luteum fails and levels of steroids and inhibin decline, this triggers a release of FSH which stimulates follicle growth in the next cycle. A number of follicles start to grow, and around day five of the menstrual cycle a number of antral follicles up to 10 mm may be present. These follicles, together with a lead follicle, produce increasing amounts of estradiol and inhibin which suppresses FSH secretion. This decline in FSH starves all but the single dominant follicle of FSH and all other follicles then die, leaving a single dominant follicle to go on to ovulate. This is a tightly regulated system to avoid high numbers of eggs being ovulated at any one time. A key issue is the regular pulsatile secretion of GnRH/LH which is an absolute requirement for normal follicle growth. We have estimated that the total amount of LH released during the day due to pulsatile secretion of LH releases about 5% of the total LH stored in the pituitary. Equally important is the amount of LH required to generate the preovulatory LH surge, which, in those species in which it has been measured, constitutes 60 to 80% of the total amount of LH present in the pituitary. The co-ordination of the patterns of secretion of LH and FSH is crucial for normal reproductive function during the menstrual cycle. Inadequate FSH will lead to inadequate induction or maintenance of follicle growth; inadequate pulsatile LH will lead to an absence of sufficient estradiol secretion to generate a preovulatory GnRH/LH surge, thus blocking ovulation. In addition, inadequate LH released either during the preovulatory LH surge or in the luteal phase may lead to inadequate corpus luteum function and a failure to maintain a pregnancy. All these possibilities occur during the suppression and subsequent return of fertility in breastfeeding women and the timing of these events is directly related to the suckling stimulus.

Earliest Time to Resumption of Fertility

During pregnancy the high level of placental steroids feedback on the hypothalamo-pituitary axis and lead to an almost complete shutdown of the synthesis and release of GnRH, which in turn leads to a suppression of the synthesis and release of LH and FSH in the immediate postpartum period. The maximum rate of recovery from this suppression due to pregnancy, which will allow the resumption of fertile menstrual cycles, can be assessed by monitoring the changes which occur if a mother chooses not to breastfeed. Within two weeks of birth, there is a resumption of a limited pulsatile LH secretion and a return to near normal levels of FSH. As a consequence, there is a small increase in the secretion of estradiol indicating limited ovarian follicle growth. Normal pulsatile secretion of LH can resume by four weeks, with a first menses within five to seven weeks. However, in the majority of cases, this first period of bleeding is preceded by an absence of ovulation, or the formation of an inadequate corpus luteum secreting small amounts of progesterone. This pattern of steroid and ovarian activity is associated with the release of a reduced amount of LH during the preovulatory LH surge. This may be a consequence of an inadequate amount of LH in the pituitary, due to the delay in synthesis of adequate amounts of LH, an insufficient amount of estradiol released by the follicle, or an inadequate release of GnRH during the preovulatory surge. It is not clear which factors are key, but the principal message is that within six to eight weeks postpartum, the key elements of the fertile normal menstrual cycle have been re-established in the absence of suckling. Indeed inter-birth intervals as short as ten months have been recorded. Suckling clearly delays this rate of return of fertility.

The Suckling-induced Suppression of Fertility

It is now clear that it is the suckling stimulus of the baby that is the key factor which suppresses fertility during breastfeeding. We also have a reasonable concept of how this suppression occurs at different levels of the reproductive axis. During exclusive breastfeeding the suckling stimulus disrupts the frequency of pulsatile secretion of GnRH from the maternal hypothalamus. As a consequence, the pattern of pulses of LH required to induce normal secretion of estradiol from the developing follicle is not sustained. Furthermore, the GnRH pulsatile release mechanism – pulse generator – is highly sensitive to estradiol, and low levels of estradiol that in the normal menstrual cycle have little effect on pulsatile GnRH release, can dramatically suppress pulsatile GnRH and hence LH secretion. During this time the pituitary remains sensitive to GnRH, and the ovaries remain responsive to gonadotrophin stimulation, indicating that the suppression of fertility does not involve effects at either the pituitary or ovary. Replacement of a pulsatile pattern of GnRH in women with lactational amenorrheoa who are exclusively breastfeeding results in a return of normal ovulatory menstrual cycles, confirming our concept that the principal effect of suckling is to disrupt the normal pattern of GnRH secretion. The mechanisms in the hypothalamus whereby the suckling stimulus suppresses the GnRH pulse generator are unknown, but in women do not appear to involve opioids or dopamine. Thus variations in the suckling pattern will have a dramatic effect on the rate of return of reproductive activity in the mother. However, the crucial issue is what or who precipitates this change in suckling activity.

Milk Production, the Suckling Stimulus and Resumption of Fertility

A major problem with giving guidance as to the amount of suckling that is required to maintain the suppression of fertility is the immense variation in the suckling stimulus itself, and the pattern

of suckling adopted by each mother infant pairing during exclusive breastfeeding. There appear to be no clear patterns emerging from monitoring infant feeding patterns, in relation to the return of fertility, which vary considerably in different societies. In studies in Scotland, Sweden and the USA, it appears that a minimum frequency of suckling can be defined which will sustain infertility in the mother, but these norms are not a universal standard. Indeed, we all know that frequencies of feeding vary dramatically amongst individual mother baby pairs during exclusive breastfeeding, and all will suppress fertility equally effectively. Certainly studies in animals have shown that increasing the suckling stimulus, e.g., in rats, by replacement of older litters with newborn litters, prolonged the duration of infertility in the mothers. However, despite several valiant efforts, there is no good simple measure of suckling strength of the baby, and particularly not that required for suppression of fertility. Nevertheless, even in the absence of any good evidence for the strength of the suckling stimulus required to maintain suppression of fertility, frequencies less than five times per day appear to allow the resumption of fertility. However, since a frequency this low is unlikely to occur during exclusive breastfeeding, this may not be an issue. Certainly there are individual reports of higher frequencies of suckling being associated with an earlier return of fertility, but it appears in this situation that the duration of each suckling episode is short, due to an extremely efficient milk-ejection system established within the mother/baby unit.

This then poses the major question of who determines the frequency of suckling, the baby or mother? Studies in red deer have shown that the frequency of suckling initiated by the offspring increases if milk production is low. In this case the calves were increasing the frequency to gain sufficient nutrition for survival. In well-nourished deer with copious milk supply calves suckled much less frequently, resulting in an earlier onset of reproductive activity. There have been no directly comparable studies in women, but it is quite possible that the apparent small effects of poor nutrition in delaying the resumption of fertility may be related to a subtle change in suckling patterns. If low milk production indicates a poor nutritional state of the mother, then it could be an indirect advantage to the mother to continue breastfeeding to maintain infertility. This would then prevent the undernourished mother having to maintain one sibling while being pregnant with another, hence increasing the nutritional load on the mother. Indeed it is clear that undernourished mothers regain lost body weight after breastfeeding provided that the inter-birth interval is sufficiently long for her to replace her reserves. This may relate to the observation that mothers may reduce their metabolic rate during lactation thus requiring less energy to make milk and sustain a normal healthy body. Certainly the baby is unlikely to reduce the suckling input in the face of poor nutrients since this would have a detrimental effect on the health of itself.

The overall conclusion would seem to be that the baby adjusts its suckling frequency and pattern of suckling to ensure sufficient nutrient intake. Whether this is done with any regard to the suppression of fertility is totally unclear. Certainly in our experience, whenever supplements are introduced, the effects on fertility in the mother is dependent on the impact the supplements have on the pattern of suckling. In most cases there is no change in the frequency of suckling, but a reduction in the duration of each feed, unless of course, the supplements were introduced as part of a weaning strategy. If the duration declined rapidly, then even with the maintenance of frequency, fertility resumed in the mother. The impact of supplements has been a matter of debate and the effects seem to depend on the nutritional value of the supplement provided, and obviously, on the frequency with which they are given, but principally on the effect on suckling

behavior of the baby. Thus any assessment of the risk of supplements affecting fertility must be taken at a local level.

What these observations do appear to indicate is that:

- the mother does not directly regulate her reproductive status to suit her baby, but responds to the suckling influence of the baby;
- a wide variation in the pattern of suckling during exclusive breastfeeding will result in a maintenance of infertility in the mother; and
- the timing of resumption of fertility is not within the control of the mother if the baby continues to suckle.

Thus, it appears that the baby is the crucial controller of the continued period of infertility in the mother. If the mother weans the baby abruptly, or the baby dies, then the reproductive axis of the mother is ready for immediate resumption, and pregnancies can occur very soon after weaning. Of course if the baby is weaned then it still has around nine more months of maternal care before there is any rivalry from a new younger sibling, and this extra time may prove very important to the well being of the baby.

Is There a Reproductive Time for the Cessation of Full Breastfeeding?

The Mother:

It appears that the maternal reproductive axis responds passively to the suckling infant, and there is no clear active suppression induced from the maternal side, even in the case of poor maternal nutrition. Thus an absolute duration of infertility associated with breastfeeding that provides reproductive benefit to the mother is not evident. However, it would clearly be of benefit to the mother not to be pregnant and exclusively breastfeeding at the same time both from the effects on the mother's and the baby's well-being. Since exclusive breastfeeding is usually associated with a complete absence of fertility, and this can be maintained for at least six months, the indirect benefit of the suppression of fertility is to give at least an 18 month inter-birth interval. However, since the maternal reproductive axis can be switched on within seven days of weaning, it is clear that there is a reproductive drive to reproduce that is held in check by the suckling baby, and it is biologically important to maintain this at a high state of readiness for conception. The ability of the reduced suckling stimulus to induce periods of inadequate luteal function which would be unable to sustain a pregnancy further emphasizes that the maternal axis is not in control of the duration of infertility during breastfeeding.

The Baby:

From a reproductive angle there are no major milestones in the neonatal period that appear to require maternal suppression of fertility. When babies are bottle fed there is no evidence of any consequences in terms of their reproductive capacity in adult life, although this has not been studied extensively. Certainly for the good health of the growing baby it is important to maintain a single contact between the baby and its mother during the early years. By suckling the baby certainly is in control of the suppression of fertility of the mother. Thus the baby is also principally in control of the duration of the period of infertility. In terms of any relation between

the reproductive axis in the baby and the duration of breastfeeding there seems to be no interactions of note since the reproductive axis of the female neonate is almost quiescent. In male infants it now appears that there is a continued low level activity of development in the testes which could possibly be compromised if inappropriate supplements were given as well as or instead of breast milk. This will require considerably more research before the true level of risk, if any, is identified for infant boys.

Conclusions

Exclusive breastfeeding in most societies is associated with a complete suppression of fertility in the mother. This suppression arises almost entirely from the suckling stimulus, with little direct maternal influence. Certain factors which influence maternal milk supply may indirectly influence suckling behavior, for instance low milk supply leading to increased suckling stimulus and further suppression of fertility, but in the main, the maternal reproductive axis responds in a passive manner to the suckling stimulus.

Indirectly there may be issues related to any supplements that may be given if exclusive breastfeeding is not maintained. There is evidence in some species that factors given in neonatal life may influence reproductive health in adults. At present there is no evidence for any major effects in humans, but studies in other primates suggest that exposure to low doses of some factors such as estrogenic compounds may affect the development of the male reproductive tract. These studies will require considerable further work before there is hard evidence one way or the other regarding the influences in humans.

From a reproductive aspect in both the mother and baby, there appears to be no specific influence of exclusive breastfeeding that can be related to a recommended absolute duration of breastfeeding. The maternal reproductive axis is programmed to return to normal rapidly when the suckling stimulus declines, and for the baby, the principal need to suppress fertility is to delay the arrival of a rival sibling. However, these are consequences which are unrelated to the reproductive axis in the baby.

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Summary and Conclusion

In the course of these reviews contributors selected articles of their own choosing. A total of 125 articles were examined, 34 regarding immunologic development, 36 regarding gastrointestinal development, 33 regarding maternal reproductive physiology and lactation, and 13 related to oral motor function. As noted, reviewers were each asked to draw independent conclusions concerning the age of developmental readiness in their particular area of expertise. They then read the papers of all other authors. The teleconference provided an opportunity for joint discussion of all four papers and consideration of the original questions.

The expert reviewers noted the lack of longitudinal studies that could be used to respond to the questions posed by these reviews, especially with regard to immunologic and gastrointestinal development. In spite of this deficiency however, the group noted certain well-evidenced points pertinent to the optimal duration of exclusive breastfeeding. Exposure of the infant to pathogens that commonly accompany food frequently results in symptomatic infection. Illness reduces the ability of the infant to suckle effectively, thus reducing the amount of milk consumed and the transfer of immune substances from mother to infant. Reduced demand from ill infants results in reduced lactation and may increase maternal risk for return of fertility. Thus, exclusive breastfeeding to about six months allows the infant greater immunologic protection and limits exposure to pathogens at a vulnerable age. This in turn permits the energy and nutrients that might otherwise be diverted to provide for immunologic responses to be available and utilized for other growth and developmental processes.

Though reports of results of formally designed longitudinal studies of oral motor function are also limited, the development of this function has been observed and described for many years by specialists in oral motor function and malfunction as well as pediatric neurologists. These clinical reports indicate that the majority of normal full term infants are not developmentally ready for the transition from suckling to sucking or for managing semi-solids and solid foods in addition to liquids until between six and eight months of age.

Considerable work has been carried out concerning the relationship of lactation to maternal reproductive physiology and the return of maternal fertility. (Lactational amenorrhea is now understood as an effective modern family planning method to be considered as an option for the first six months post-postpartum, if the guidelines are understood and followed). It is clear that milk production is largely an infant driven physiology. Under most circumstances, during the period of exclusive breastfeeding, mothers will provide what the infant requires, assuming that the infant is allowed to nurse as needed. Exclusive breastfeeding with a frequent nursing pattern is very likely to maintain infertility, lengthening the time between pregnancies and allowing a mother to give her full biologic, cognitive and emotional attention to the particular infant.

Using the available information on the development of infant's immunologic, gastrointestinal and oral motor function, as well as maternal reproductive physiology, the expert review team concluded that the probable age of readiness for most full term infants to discontinue exclusive breastfeeding and begin complementary foods appears to be near six months or perhaps a little beyond. They also felt that there is probable convergence of such readiness across the several relevant developmental processes.

The consensus opinion of the expert review group was that given the available information and the lack of evidence of significant harm to either normal mothers or normal infants, there is no reason to conclude that exclusive breastfeeding should not continue to six months.

The expert reviewers noted the need for longitudinal studies to allow for a more careful examination of the very questions posed by this effort, particularly with regard to immunologic and gastroenterologic processes. Given the global implications for maternal and infant health, gaps in scientific knowledge identified in these reviews should be considered as priority topic areas for future research funding.

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